A Phase 1, Open-Label, Multicenter, Drug-Drug Interaction Study of TAK-788 and Midazolam, a Sensitive CYP3A Substrate, in Patients With Advanced Non*Small Cell Lung Cancer

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Primary Objectives:The primary objective of this study is to characterize the effect of repeated oral administration of TAK-788 160 mgQD on the single oral- and IV-dose PK of midazolam.Secondary Objectives:The secondary objective of this study is to...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Respiratory and mediastinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON49519

Source
ToetsingOnline

Brief title
Drug-Drug Interaction Study

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
Lung cancer, lung tumor

Research involving
Human

Sponsors and support

Primary sponsor: Millenium Pharmaceuticals
Source(s) of monetary or material Support: by the sponsor Millennium Pharmaceuticals;Inc.;a wholly owned subsidiary of Takeda Pharmaceutical Company Limited

Intervention

Keyword: Non-Small Cell Lung Cancer, Open-Label, TAK-788

Outcome measures

Primary outcome

Main Criteria for Evaluation and Analyses:

The primary endpoints of the study include, but are not limited to the

following midazolam PK parameters after oral

or IV administration in the presence and absence of TAK-788:

Primary Endpoints

* The geometric mean ratios and 90% CI of Cmax and AUC* for midazolam

administered orally with TAK-788

and when orally administered as midazolam alone.

* The geometric mean ratios and 90% CI of Cmax and AUC* for midazolam

administered intravenously with

TAK-788 and when intravenously administered as midazolam alone

Secondary outcome

Secondary Endpoints

The secondary endpoints of the study encompass the safety profile of TAK-788

and are as follows:

* AEs.

* Clinical laboratory tests (hematology and clinical chemistry).

* Vital signs.

Study description

Background summary

TAK-788 is an investigational drug which means that it is not approved yet by FDA or/and any other Regulatory Agency across the world. It is a novel drug which has potency to substantially reduces activity of one of the tyrosine kinases * a category of protein (enzyme) playing important roles in development of the tumors including NSCLC (Non Small Cell Lung Cancer) which you are suffering from. TAK-788 will be tested during this study to evaluate for effectiveness on the types of NSCLC which relapsed or spread to other regions of your body after the routine treatment (such as chemotherapy or radiotherapy) so is considered resistant to the types of treatment which were used so far. Midazolam is approved by the US FDA (United States Food and Drug Administration) for anesthesia, sedation, trouble sleeping, and severe agitation. In the Netherlands it is approved for anesthesia, sedation and trouble sleeping.

Study objective

Primary Objectives:
The primary objective of this study is to characterize the effect of repeated oral administration of TAK-788 160 mg
QD on the single oral- and IV-dose PK of midazolam.

Secondary Objectives:
The secondary objective of this study is to assess the safety and tolerability of TAK-788 in patients with advanced
NSCLC.

Study design

Study Design:
This open-label, multicenter, drug-drug interaction study will consist of 2 parts: Part A (Cycle 1: PK Cycle) and Part
B (Cycle 2 to Cycle 24: Treatment Cycles).
In Part A of the study, a fixed-sequence design over a single 30-day treatment cycle will be used (Cycle 1: PK Cycle
and Cycle 2 Day1). After screening, eligible patients will be enrolled and will receive a single oral dose of
midazolam 3 mg on Days 1 and 24 and a single IV dose of midazolam 1 mg as a 5-minute infusion on Days 2 and

25. Patients will also receive TAK-788 160 mg QD orally on Days 3 through 30. Serial PK blood samples will be
collected to measure plasma concentrations of midazolam and its metabolite 1-hydroxymidazolam in the absence
and presence of TAK-788 on study Days 1, 2, 24, and 25. TAK-788 PK blood samples to assess TAK-788 plasma
concentrations and its active metabolites AP32960 and AP32914 will be collected predose on Days 24, 25, and 26 of
cycle 1 as well as Day 1 of cycle 2 and postdose on Cycle 1 Day 24.
Further, biomarker blood samples will be collected on Days 1 and 24 predose to measure plasma concentrations of
4*-hydroxycholesterol and cholesterol, in addition to samples collected to assess for circulating tumor DNA as part
of Cycle 1, 3, 5, and disease progression assessments.
After completion of Part A, patients may continue into Part B to to continue treatment with TAK-788 (Cycle 2 to
Cycle 24: Treatment Cycles). Any patients who are not PK-evaluable due to incomplete PK sample collections in
Part A will be eligible to continue into Part B.
Part B of the study will consist of 28-day treatment cycles in which patients will continue to receive TAK-788 QD
for up to 23 months (ie, Cycle 24) or until progressive disease, intolerable toxicity, or another discontinuation
criterion is met, whichever is sooner.
TAK-788 dose may be reduced based on protocol-defined dose modification guidelines during the study. Safety and
tolerability will be evaluated during the study by AE monitoring, clinical laboratory tests, vital signs, and physical
examinations. The study will include a 30-day follow-up period after EOT for reporting of AEs.
Exploratory radiological disease assessments will be performed by contrast-enhanced computed tomography (CT)
and/or magnetic resonance imaging (MRI) (unless contrast media is contraindicated) at 8-week intervals during
treatment through Cycle 14; radiological assessments will then be performed every 12 weeks (ie, every 3 cycles)
thereafter, and at EOT. Imaging of the brain (contrast-enhanced MRI is preferred) is required at screening for all
patients, and will be repeated post-baseline for patients with CNS metastases at baseline.

Intervention

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Study burden and risks

see section E9.

Contacts

Public
Millenium Pharmaceuticals

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Scientific
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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Male or female patients aged *18 years.
2. Histologically or cytologically confirmed locally advanced NSCLC in which the patient is not a candidate for definitive therapy; or, the patient has recurrent or metastatic (Stage IV) disease.
3. Refractory or intolerant to standard available therapies.
4. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1.
5. Minimum life expectancy of 3 months or more.
6. Adequate organ function as defined by the protocol criteria.
a) Total serum bilirubin *1.5 × upper limit of normal (ULN) (*3 × ULN for

patients with Gilbert syndrome or if liver function abnormalities are due to underlying malignancy);
b) Alanine aminotransferase and aspartate aminotransferase *2.5 × ULN (or *5 × ULN if liver function abnormalities are due to underlying malignancy);
c) Estimated creatinine clearance *30 mL/min (calculated by using the Cockcroft-Gault equation);
d) Serum albumin *2 g/dL;
e) Serum lipase *1.5 × ULN; and
f) Serum amylase *1.5 × ULN unless the increased serum amylase is due to salivary isoenzymes.
7. Adequate bone marrow function, as defined by the protocol criteria.
a) Absolute neutrophil count *1.5 × 109/L;
b) Platelet count *75 × 109/L; and
c) Hemoglobin *9.0 g/dL.
8. Normal QT interval on screening ECG, defined as QTcF of *450 msec in males or *470 msec in females. (as conducted and interpreted in accordance to local institutional practices and confirmed by PI).
9. All toxicities from prior anticancer therapy must have resolved to *Grade 1 according to the NCI CTCAE version 5.0 [1], or have resolved to baseline, at the time of first dose of TAK-788. Note: treatment-related Grade 2 or 3 alopecia and treatment-related Grade 2 peripheral neuropathy are allowed if deemed irreversible.
10. Female patients who are of childbearing potential, agree to comply with protocol-defined contraception criteria or practice true abstinence.
11. Male patients agree to practice effective barrier contraception during the entire study treatment period and through 30 days after the last dose of study drug, or agree to practice true abstinence.
12. If female, a negative serum or urine pregnancy test result during the screening period.
13. Suitable venous access for study-required blood sampling (ie, including for PK, pharmacodynamics, and clinical laboratory tests).
14. Willingness and ability to comply with scheduled visits and study procedures.
15. Signed and dated the informed consent indicating that the patient has been informed of all pertinent aspects of the study. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

Exclusion criteria

1. Previously received TAK-788.
2. Received a strong or moderate CYP3A inhibitor or strong or moderate CYP3A inducer within 2 weeks prior to the first dose of TAK-788.
3. Received small-molecule anticancer therapy (including but not limited to

cytotoxic chemotherapy and investigational agents) within 2 weeks prior to the first dose of TAK-788.
4. Received antineoplastic monoclonal antibodies including check point inhibitors within 28 days of the first dose of TAK-788.
5. Received radiotherapy *14 days prior to the first dose of TAK-788. However, patients are allowed to receive any of the following treatments up to 7 days prior to the first dose: (a) Stereotactic radiosurgery (SRS), (b) stereotactic body radiation therapy (SBRT), or (c) palliative radiation outside the chest and brain.
6. Major surgery within 28 days prior to the first dose of TAK-788. Minor surgical procedures, such as catheter placement or minimally invasive biopsy, are allowed.
7. Diagnosed with another primary malignancy other than NSCLC except for adequately treated non-melanoma skin cancer or cervical cancer in situ; definitively treated non-metastatic prostate cancer; or another primary malignancy and is definitively relapse-free with at least 3 years elapsed since the diagnosis of the other primary malignancy.
8. Have known active brain metastases (have either previously untreated intracranial CNS metastases or previously treated intracranial CNS metastases with radiologically documented new or progressing CNS lesions). Brain metastases are allowed if they have been treated with surgery and/or radiation and have been stable without requiring corticosteroids to control symptoms within 7 days before the first dose of TAK-788, and have no evidence of new or enlarging brain metastases.
9. Current spinal cord compression (symptomatic or asymptomatic and detected by radiographic imaging) or leptomeningeal disease (symptomatic or asymptomatic).
10. Have uncontrolled hypertension. Patients with hypertension should be under treatment on study entry to control blood pressure.
11. Significant, uncontrolled, or active cardiovascular disease.
12. Treatment with medications known to be associated with the development of torsades de pointes.
13. Current or history of interstitial lung disease, radiation pneumonitis that required steroid treatment, or drugrelated pneumonitis.
14. Ongoing or active infection including, but not limited to, the requirement for IV antibiotics, or a known history of human immunodeficiency virus infection. Testing is not required in the absence of history. Patients who are positive for hepatitis B surface antigen or anti-hepatitis C virus antibody may be eligible (see full protocol for further details).
15. Gastrointestinal illness or disorder that could affect oral absorption of TAK-788 or midazolam.
16. If female, the patient is lactating and breastfeeding. Female patients who are lactating will be eligible if they discontinue breastfeeding.
17. History of, or suspected, hypersensitivity or allergy to midazolam or its excipients or TAK-788.
18. Any condition or illness that, in the opinion of the investigator, might compromise patient safety or interfere with the evaluation of the safety of the study drug.

19. Admission or evidence of illicit drug use, drug abuse, or alcohol abuse.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-06-2020
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	midazolam
Generic name:	na
Product type:	Medicine
Brand name:	TAK-788
Generic name:	na

Ethics review

Approved WMO Date:	22-07-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	06-03-2020

Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	14-05-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-05-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-06-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-07-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	02-11-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-05-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	20-07-2021
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2019-000725-44-NL
CCMO	NL70465.031.19